Growth promoting hormones and antler development

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Abstract. Cell, tissue and organ growth is largely under the control of a variety of circulating and local hormones. The major circulating growth endocrine system of growth hormone (GH) release which in turn stimulates insulin-like growth factors (IGF) has been studied in red deer stags. GH is strongly pulsatile during late winter to early summer with about 4 large amplitude pulses each day. For the rest of the year GH is episodic although large distinct pulses are not apparent. The large pulses are thought to stimulate IGF_1 secretion from the liver. Peak plasma levels of IGF_1 occur in early summer and correlate very closely with velvet antler growth and antler size.

A number of growth factors have been isolated from cell and tissue types similar to those found in antlers and well informed speculation about their role in controlling antler growth is possible.

IGF_1 is not capable of making cells competent for cell division and it is considered that a hormone such as platelet derived growth factor must be responsible for this. Neither has IGF any known specific effect on blood vessels, nerves or the epidermis. Instead we speculate that angiogenic factor, nerve growth factor and epidermal growth factors for fibroblasts, chondroblasts (cartilage) and osteoblasts (bone) are known; we speculate that they will exist in the antler.

There is no single antler stimulating hormone; instead of tapestry of regulating hormones has been woven. The ultimate identity of these and the trophic stimuli controlling them largely remain the mystery.

The velvet antler is composed of fibroblasts, chondroblasts, chondrocystes, osteoblasts, osteocystes and clastic cells (Banks and Newbrey, 1982). In tissues such as foetal cartilage and bone, the growth and differentiation of these cells is known to be associated with a variety of circulating and local growth promoting hormones and growth factors. It seems logical when searching for the hormones which regulate antler development to measure those which are known to promote growth in cells and tissues like those found in the antler.

This paper reviews the data from studies which have measured circulating growth promoting hormones in deer, namely growth hormone (GH) insulin like growth factors (IGF) and steroids and then speculates on the local growth factors which may be involved with antler growth.

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Circulating hormones in deer

GH

Bubenik et al. (1974) measured GH in single blood samples from white tailed deer *Odocoileus virginianus* and found maximal levels in spring just prior to velvet antler development. However, levels declined dramatically during antler development. Ryg and Langvatn (1982) found peak GH levels in red deer *Cervus elaphus* in spring, but Barrell et al. (1985) found peak levels in autumn during the period of peak weight loss. Suttie et al. (in press) measured secretion of GH in samples taken every 30 minutes over a 26-h period each month in red deer stags from 4-15 months of age. They found that GH was released in a pulsatile manner in every month of sampling, but that the pattern of pulsatility differed seasonally. During autumn and early winter GH pulses were frequent but of low amplitude. In contrast, in spring, GH pulses were of high amplitude and high frequency resulting in a high mean level of GH circulating in the plasma. In summer GH pulse amplitude was much lower, and pulse frequency fell. There was a rise in GH pulse frequency not accompanied by an increase in pulse amplitude in late summer. GH pulse amplitude was the major determinant of mean GH plasma Level. GH correlated positively and significantly with antler growth rate measured one month later.

Although there is some indication from the literature (Isaksson et al., 1982; Madsen et al., 1983), that GH stimulates bone growth directly *in vivo* and *in vitro*, Schoenle et al. (1985) consider that the major bone growth promoting role of GH is via the IGF's.

IGF

IGF_1 secretion, but not IGF_2, correlates significantly and positively with antler growth (Suttie et al., 1985; Suttie et al., in press). In addition, in the second study, plasma IGF_1 was correlated with mean plasma GH level recorded one month earlier. As it is known in laboratory animals that GH stimulates IGF_1 release (Furlanetto et al., 1977), it is concluded that the antler stimulating IGF_1 is released due to stimulation from GH. It is proposed that the strong pulsatile secretion of GH measured in spring results in IGF_1 secretion which stimulates velvet antler growth.

Steroids

There is little doubt that the timing of the antler cycle in relation to photoperiod and the process of antler mineralisation is under the control of circulating levels of testosterone (Bubenik, 1982). However the extent to which steroids modify velvet antler growth is not clear. Although receptors for testosterone have been found in velvet antler (Bubenik et al., 1974), *in vitro* studies with fetal rat calvaria revealed that testosterone had no growth promoting effect on cartilage (Canalis and Raisz, 1978). It is known in male sheep that testosterone is responsible for the pulsatile secretion of GH presumably via a mechanism involving GHRH (Davis et al., 1977). It could be that testosterone excepts a stimulatory role over the antler growth by modifying GH secretion. Jansson et al. (1983), who studied rat bone growth, concluded that testosterone exerted its main stimulating effect by altering the secretory pattern of GH. However, as testosterone may act synergistically with IGF_1 to regulate human growth (Luna et al., 1983), a possible role of low levels of steroids during antler development cannot be overlooked. Indeed Bubenik (1982) correlated very low levels of testosterone with extent of antler growth in castrated deer. An alternative explanation for reduced antler size in castrated male deer is that the testis may be source of IGF_1. Castration in red deer reduces plasma IGF_1 levels (J.M. Suttie, unpublished observations).

In conclusion circulation steroids appear to exert their major effect on antler growth indirectly via GH or IGF_1.

Local growth factors and the antler speculation from other species

Platelet-deriveds growth factors (PDGF)

PDGF is a heat stable polypeptide transported in the blood by platelets and released during blood clotting (Antoniades and Williams, 1983). Quiescent BALB/c3T3 cells exposed to PDGF became competent to replicate their DNA and divide (Stiles et al., 1979).

It is suggested that PDGF could play a role in making quiescent antler fibroblasts competent for cell division, which is then stimulated by IGF_1.

Fibroblast growth factor (FGF)

Basic FGF which can be isolated from bovine pituitaries is found in a variety of tissues, is angiogenic *in vivo* (Esch et al., 1985) and is capable of making fibroblasts competent for cell division (Clemmons, 1984). Canalis and Raisz (1980) found that the major effect of FGF in foetal rat calvaria was to increase DNA synthesis and stimulate the proliferation of periosteal fibroblasts.

FGF could play at least two possible roles in antler growth. It could stimulate the rapid turnover of the capillary bed at the growing tip of the antler, and it could operate synergistically with PDGF to make antler fibroblasts competent for cell division.

Cartilage derived growth factor (CDGF)

Foetal bovine cartilage contains a polypeptide which stimulates incorporation of

^{35}S and ^{3}H-thymidine into proteoglycans synthesised by rat costal chondrocytes (Kato et al., 1981). Bekoff and Klagsbrun (1982) found about five times as much growth factor activity in the extracelluar matrix than the chondrocytes in human costal cartilage *in vitro*. The relevance of these results for the antler is probably that growth factors specific to cartilage regulate the differentiation, multiplication and growth of chondroblasts and chondrocytes. Although these factors have not been located in the antler it is highly likely, they, or similar growth factors, will be found.

Bone morphogenic protein (BMP) and bone derived growth factors (BDGF)

BMP is a glycoprotein which irreversibly induces differentiation of perivascular mesenchymal cells into osteoprogenitor cells. BDGF is secreted by and for osteoprogenitor cells and stimulates DNA synthesis (Urist et al., 1983). Implants of bone matrix containing BMP and BDGF are mitogenic and promote chondrogenesis and osteogenesis *in vivo*, but BMP is active in stimulating mitotic activity some days before BDGF is produced (Urist et al., 1983). As for CDGF, BMP and BDGF could play a role in antler chondrogenesis and osteogenesis.

Epidermal growth factor (EGF)

EGF has growth stimulating activity for a variety of call types and stimulates the proliferation and keratinisation of epidermal tissues (Bertsch and Marks, 1974). EGF stimulates DNA synthesis in bone and inhibits bone cartilage synthesis *in vitro* (Canalis and Raisz, 1979). EGF has been purified from cartilaginous antler tips (Ko et al., 1986).

It seems likely that EGF's primary role in the antler is to stimulate epidermal growth and possibly also hair follicle and hair production.

Nerve growth factor (NGF)

Antler nerves must grow rapidly to keep pace with the antler. As NGF is essential for the survival and differentiation of sympathetic and sensory neurones in the foetus (Levi-Montalcini and Angeletti, 1968), it seems likely that it is essential for the development of antler nerves.

Angiogenic factors

Transforming growth factors (TGF) are structurally related to EGF, and both these factors promote angiogenesis *in vivo* with receptors being found in endothelial cells; TGF is more potent than EGF (Schreiber et al., 1986). In addition TGF assists with wound healing (Shultz et al., 1986). In the antler, angiogenic factors would be involved with the turnover of the vascular bed at the growing tip.

Negative regulators of cell growth

Endogenous inhibitors of cell growth have been purified from tissues and cell lines. There is a lot of current research investigating their role in cellular and tissue homeostasis and growth (Wang and Hsu, 1986). In the antler, cell growth inhibitors could limit antler size and assist with development of the species specific shape.

Conclusion

It is highly likely that there is no single antler stimulating hormone but a variety of circulatory and local hormones are involved with antler growth regulation. It can be speculated that cell competence factors like PDGF must first prepare progenitor cells for division and growth, and then the progression factors like IGF_1 advance cell division and growth. Individual tissue growth factors have local control over differentiation whether the tissues are ultimately structural, eg., cartilage and bone, or whether they are supportive or nutritive,

eg., nerves or blood vessels. Presumably the overall control of antler growth is genetic, although the overall control of the development of growth factors to stimulate antler growth is unknown. In that many of the local tissue growth factors described above have been discovered in tumours, and several parallels can be drawn between tumours and antlers (Goss, 1983), the ultimate goal of antler growth factor research must be to assist our understanding of that crippling disease-cancer.

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